REMARKS

Claims 17-32 are currently pending in this application. Claims 17-27 and 29-32 have been withdrawn from further consideration as being drawn to non-elected subject matter. In light of the amendments to claims 17-20, 24, 26 and 32, Applicants respectfully request that these claims be rejoined and considered because they now depend from and further limit elected claim 28. The Applicants expressly reserve the right to file one or more divisional applications directed to the non-elected subject matter.

According to the Office Action of March 26, 2008, claim 28 has been examined on its merits, and has been rejected under 35 U.S.C. § 112, first paragraph, enablement requirement; 35 U.S.C. § 112, first paragraph, written description requirement; and 35 U.S.C. § 103. In addition to these rejections, the Office Action objects to the abstract, and objects to the Information Disclosure Statement. In view of the amendments to the abstract and the remarks below, the Applicants respectfully request reconsideration and withdrawal of the asserted objections and rejections.

OBJECTION TO THE ABSTRACT

In view of the amendment to the abstract, Applicants respectfully request that the objection asserted against the abstract be withdrawn.

INFORMATION DISCLOSURE STATEMENT

On page 3, the Office Action states that WO 00/62753 was not considered because the Applicants did not provide a concise explanation of the relevance of this reference. While this reference is not in English, it contains a partial English translation – a translation of the abstract. According to MPEP § 609.04(a), "[s]ubmission of an English language abstract of a reference may fulfill the requirement for a concise explanation." Since WO 00/62753 contained a translation of the abstract, which may fulfill the requirement of a concise explanation, Applicants respectfully request that WO 00/62753 be considered by the Examiner.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

Claim 28 has been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification with regard to a method of preventing vaginal dryness. When asserting an enablement rejection, the Examiner bears the burden of setting forth a reasonable explanation as to why he or she believes that the claims are not enabled by the specification. *In re Wright*, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993); *In re Stoughton*, No. 2005-2235, App. No. 09/038,894, 2006 WL 1665412 at *4 (BPAI 2006). Precise predictability is not the standard to employ. *In re Corpet*, No. 2004-1790, App. No. 09/836,971, 2004 WL 2733634 (BPAI 2004).

In *Corpet*, the examiner rejected claim 12 as not enabled by the specification. 2004 WL 2733634 at *1. Claim 12 recited "[a] method of preventing colon or rectum cancer comprising administering to a mammal a therapeutically effective amount of a non-fermented osmotic polyol laxative." *Id.* The rationale for rejecting claim 12 was based on the argument

> that the recitation of preventing "extend[s] the treatment to those patients in which rectal and colon cancers may occur at any point of time in [the] future." [Citation omitted.] With respect to the state of the art, the examiner apparently recognizes that "[t]he state of the art recognizes that increased intake of dietary fibers contribute to the increased bowel movements and thus result in lowering the risk of colon cancers," but asserts that "the art does not teach or recognize a complete prevention of the above claimed cancers." [Citation omitted.] Finally, with respect to guidance of the specification and examples, the examiner focuses on the lack of teaching of an understanding of when the cancer may occur.

Id. at *1. The Board determined that the examiner's rationale required "precise predictability as to the time when the colon or rectal cancer will appear, and also appears to require 100% prevention. That is not, however, a requirement under 35 U.S.C. § 112, first paragraph." *Id.* at *2. Due to this flawed rationale, the Board held that the examiner failed to meet his burden and reversed the rejection. *Id.* at *3.

The Board reversed a similar rejection in *In re Goldenberg*, App No. 08/183,381, 2002 WL 31105508 (BPAI 2002). In *Goldenberg*, the examiner argued that "'[a]pplicant [sic] broadly claims [sic] an anti-idiotype vaccine to prevent cancer, AIDS and malaria, but the specification fails to enable the vaccine(s) and effectively teach how to make and/or use said vaccines to achieve this.'" *Id.* at *3. The Board held that this

> failed to provide the evidence necessary to demonstrate that appellants' disclosure does not enable their claimed invention. While some of the claimed combinations may be inoperative, the examiner failed to establish that the number of inoperative combinations is so significant, that one of ordinary skill in the art would have to experiment unduly in order to practice the claimed invention.

Id. at *4.

These cases establish that claims directed to preventing a disease can be enabled by a specification. Thus, there is no *per se* bar against claims directed to preventing a disease. Instead, there must be reasonable explanation why one of ordinary skill in the art would not be able to practice the invention without undue experimentation. Instead of providing the experiments necessary to establish prevention, the Office Action contends that the invention is "nearly impossible," and that "no one skilled in the art would accept the assertion that the instantly claimed estrogenic compound could be predictably used to prevent vaginal dryness."[1] This does not establish that undue experimentation is necessary to practice this aspect of the invention. It only stands for the unilateral opinion that the Patent Office does not believe that the invention is capable of preventing vaginal dryness.

The Patent Office's unilateral opinion that an aspect of an invention is inoperable is insufficient to support an enablement rejection. Instead, the Patent Office must "provide evidence necessary to demonstrate that [the Applicants'] disclosure does not enable their claimed invention." *Goldenberg*, 2002 WL 31105508 at *4. Here, there has been no evidence provided to establish that the recited and disclosed invention is inoperable.

For these reasons, it is respectfully requested that this rejection be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claim 28 has been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Claim 28 has been amended to add a methyl group at C-18. Accordingly, withdrawal of this rejection is respectfully requested.

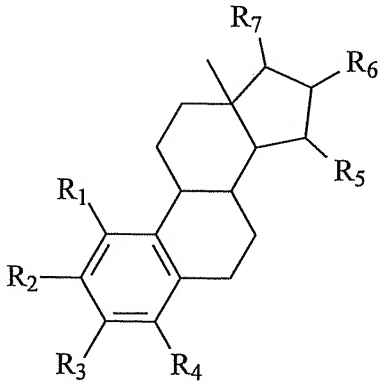
[1] Office Action at pages 5-6.

REJECTION UNDER 35 U.S.C. § 103

Claim 28 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over United States Published Patent Application Number 2004/0192598 to Kragie ("Kragie") in view of Willhite *et al.*, "Urogenital Atrophy: Prevention and Treatment," PHARMACOTHERAPY (2001) 21(4): 464-480 ("Willhite"). Claim 28 has also been rejected under 35 U.S.C. § 103(a) as being unpatentable over the abstract of Sitruk-Ware *et al.*, "Local hormonal treatment for urogenital atrophy after menopause," Schweiz. Rundsch., Med. Praxis (1997) 86(33): 1245-1248 ("Sitruk-Ware") in view of United States Patent Number 5,21,952 to Spicer ("Spicer") and Willhite. Applicants respectfully traverse these rejections because there was no reasonable expectation in the art that the recited estrogenic component would be pharmacologically active, and because it was unexpected to discover that the recited estrogenic component is pharmacologically active.

I. THE CLAIMED INVENTION

The invention as recited in claims 28 is directed to a method of treating or preventing vaginal dryness comprising applying to a composition. The composition contains at least 5 μg/g of an estrogenic component. The estrogenic component is selected from the group consisting of substances represented by the following formula:



in which formula R_1, R_2, R_3, R_4, independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; each of R_5, R_6, R_7 is a hydroxyl group; no more than 3 of R_1, R_2, R_3, R_4 are hydrogen atoms; precursors capable of liberating a substance according to the aforementioned formula when used in the present method; and mixtures thereof. In

one embodiment, the estrogenic component is estetrol. The composition also contains a cosmetically acceptable vehicle.

II. THE CITED REFERENCES

The Office Action contends that Kragie teaches using estrogen function replacement agent(s) to treat vaginal atropy, and that Willhite teaches that vaginal atropy is synomous with vaginal dryness.[2] Kragie is directed to compositions and methods to replace estrogen in humans and other animals.[3] According to Kragie's invention, this is accomplished by administering an estrogen function replacement agent(s) ("EFR agent").[4] An EFR agent "is defined as one that can selectively, totally, or partially replace the function performed by the estrogen compounds that are usually synthesized by the aromatase enzyme."[5] Kragie provides an overly broad list of EFR agents, which include: estradiol, ethinyl estradiol, estradiol valerate, estradiocypionate, estrone, estriol, estetrol, estropipate, 2-methoxyestradiol, hydroxyestrones, sodium estrone sulfate, equine estrogens, equilenin, equilin, conjugated estrogens, esterified estrogens, micronized estrogens, synthetic estrogens, nonsteroidal estrogens; phytoestrogens such as isoflavonoids, flavonoids, lignans, coumestan, and other natural compounds derived from plants such as soya, tea, fruits and vegetables; synthetic phytoestrogen ipriflavone; genistein, daidzein, enterolactone; selective estrogen receptors ligands and modulators factors (such as raloxifene, tamoxifen, indenoindoles, and estrogen partial agonist/antagonists); catechol estrogens and their metabolites (such as 2-hydroxyestrone, 2-hydroxyestradiol and their 4-hydroxy isomers); 2,3-estrogen o-quinone, diethylstilbestrol, nitro-estrogens, catechol estrogen 3,4-quinone, estrophilin, formatrix, methallenestril, quinestrol, chlorotrianisene, norethisterone, norethindrone, 17-alpha-ethynyl-19-nortestosterone; dienestrol, norethynodrel, promethestrol, mestranol, tamoxifen, hydroxytamoxifen, clomiphene, chlorotrianisene, nafoxidine, hexestrol, niifepristone, RU 486; bisphenol A, p-tert-octylphenol and other endocrine disruptors; B-ring homologated estradiol analogues; estrogen receptor elements (such as estrogen receptor activation factor,

[2] Office Action at pages 9-10.

[3] Kragie at abstract.

[4] Kragie at ¶ 13.

[5] Kragie at ¶ 13.

activated estrogen receptor complex, and Heat Shock Protein).[6] However, at the relevant time, one of ordinary skill in the art would not have picked estetrol from this long list, or even considered using estetrol when the relevant scientific literature teaches that it was believed not to be pharmacologically active.

The Office Action also contends that the combination of Sitruk-Ware, Spicer and Willhite likewise suggest the recite invention.[7] The Office Action contends that Sitruk-Ware teaches that estrogenic treatment is an efficient way to correct vaginal dryness, and that Spicer teaches the that estetrol may be employed in composition formulated for vaginal delivery.[8] Like Kragie, Spicer also provides an overly broad list of estrogens. Specifically, Spicer states that

> [n]atural and synthetic estrogenic compositions which can be used according to the invention described herein include natural estrogenic hormones and congeners, including but not limited to estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, diethylstilbestrol, piperazine estrone sulfate, ethinyl estradiol, mestranol, polyestradiol phosphate, estriol, estriol hemisuccinate, quinestrol, estropipate, pinestrol and estrone potassium sulfate. Equine estrogens, such as equilelinin, equilelinin sulfate and estetrol, may also be employed.[9]

However, there is no reason why one would pick estetrol from this long list where estetrol is listed as a mere possibility rather than part of the invention, or would consider using estetrol when the relevant scientific literature teaches that it was believed not to be pharmacologically active.

Point I. There was no reasonable expectation that estetrol would be pharmacologically active.

None of these references establish that the recited estrogenic component is pharmacologically active. Without such a disclosure, one of ordinary skill in the art would not reasonably expect estetrol to be useful in the recited method because, based on the scientific data published prior to the publication of this invention, such a person expected

[6] Kragie at ¶ 39.

[7] Office Action at page 11-13.

[8] Office Action at page 12.

[9] Spicer at column 5, lines 50-61.

estetrol not to be pharmacologically active.

Prior to the disclosure of the present invention, estetrol was believed to be a very weak natural estrogen.[10] In fact, a person of ordinary skill in the art believed that estetrol would not have any meaningful pharmacological effect due to its low estrogenic potency, and the fact that one would have expected estetrol to be similar to the natural estrogens estradiol and estriol in exhibiting a very short elimination half-life. The specification identifies several references that establish estetrol's low receptor binding affinity and poor estrogenicity:

- Levine et al., 1984. Uterine vascular effects of estetrol in non-pregnant ewes. Am. J. Obstet. Gynecol., 148:73, 735-738: "When intravenously administered in non-pregnant ewes, estetrol is 15 to 30 times less potent than estriol and 17.beta.-estradiol in uterine vasodilation".
- Jozan et al., 1981. Different effects of oestradiol, oestriol, oestetrol and of oestrone on human breast cancer cells (MCF-7) in long term tissue culture. Acta Endocrinologica, 98, 73-80: "Estetrol agonistic potency is 2% of the magnitude observed for 17β-estradiol in in-vitro cell proliferation".
- Holinka et al., 1980. Comparison of effects of estetrol and tamoxifen with those of estriol and estradiol on the immature rat uterus. Biol. Reprod. 22, 913-926: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17β-estradiol and estriol".
- Holinka et al., 1979. In vivo effects of estetrol on the immature rat uterus. Biol. Reprod. 20, 242-246: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17β-estradiol and estriol".
- Tseng et al., 1978. Heterogeneity of saturable estradiol binding sites in nuclei of human endometrium. Estetrol studies. J. Steroid Biochem. 9, 1145-1148: "Relative binding of estetrol to estrogen receptors in the human endometrium is 1.5% of 17β-estradiol".
- Martucci et al., 1977. Direction of estradiol metabolism as a control of its hormonal action-uterotrophic activity of estradiol metabolites. Endocrin. 101, 1709-1715: "Continuous administration of estetrol from a subcutaneous depot shows very weak uterotrophic activity and is considerably less potent than 17.beta.-estradiol and estriol".
- Tseng et al., 1976. Competition of estetrol and ethynylestradiol with estradiol for nuclear binding in human endometrium. J. Steroid Biochem. 7, 817-822: "The relative binding constant of estetrol binding to the estrogen receptor in the human endometrium is 6.25% compared to 17β-estradiol (100%)".

[10] See Holinka (1980), *infra* at abstract.

- Martucci et al., 1976. Uterine estrogen receptor binding of catecholestrogens and of estetrol (1,3,5(10)-estratriene-3,15alpha,16alph, 17beta-tetrol). Steroids, 27, 325-333: "Relative binding affinity of estetrol to rat uterine cytosol estrogen receptor is 0.5% of 17β-estradiol (100%). Furthermore, the relative binding affinity of estetrol to rat uterine nuclear estrogen receptor is 0.3% of 17β-estradiol (100%)".[11]

To further evidence these points, Applicants submit declarations from third-party artisans in the field, and a declaration from one of the co-inventors. As these declarations establish, prior to the publication of this invention, one of ordinary skill in the art believed that estetrol would not have been pharmacologically active.[12] This is because it was known in the art that estetrol had a substantially lower receptor affinity than estradiol or estriol.[13] Specifically, one of ordinary skill would have expected estetrol to be less effective than estradiol or estriol because Holinka (1980)[14] suggests that estetrol is a much weaker estrogen than the already weak estrogen estriol, given that estetrol injected subcutaneous at 50 µg/100 g body mass exhibited less estrogenic activity than estriol injected subcutaneous at 1 µg/100 g body mass.[15] Estriol is a very weak estrogen due to its low receptor affinity in combination with its very short half-life of 5-10 minutes.[16] Holinka (1980) teaches that estrogenic activity of estetrol is at least 50 times lower than that of a weak estrogen for which very few practical applications exists, [17] and therefore teaches away from estetrol having any significant pharmacological effect.

Additionally, a person of ordinary skill in the art would have expected estetrol to be comparable to estriol.[18] Estetrol differs from estriol by only one hydroxyl group, and

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[11] Specification at pages 4-5. Copies of these references are attached to this Amendment.

[12] See Declaration by Strauss at ¶¶ 8-9; see also Declaration by Speroff at ¶¶ 8-9; see also Declaration by Westhoff at ¶¶ 8-9; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[13] See Holinka (1980), abstract, see also Declaration by Strauss at ¶¶ 15-16, 18 and 20; see also Declaration by Speroff at ¶¶ 15-16, 18 and 20; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[14] Holinka (1980).

[15] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; see also Declaration by Westhoff at ¶16; and Declaration by Coelingh Bennink at ¶¶ 5.

[16] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; see also Declaration by Westhoff at ¶16; and Declaration by Coelingh Bennink at ¶¶ 5.

[17] Declaration by Strauss at ¶¶ 15-16; Declaration by Speroff at ¶¶ 15-16; Holinka (1979); and Holinka (1980).

[18] Declaration by Strauss at ¶ 1; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

both estriol and estetrol are produced during pregnancy.[19] Hence, one of ordinary skill in the art would have believed that estetrol, like estriol, has a very short half-life on the order of minutes.[20]

Thus, the recited invention is patentable over the cited references because one of ordinary skill in the art would not reasonably expect that he or she could successfully use estetrol since it was believed that estetrol was not pharmacologically active. When making a rejection under 35 U.S.C. § 103, the examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). As part of a *prima facie* case, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 131 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

A combination of known elements will not yield predictable results if the references teach away from the claimed invention. *Takeda Chemical*, 492 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc. v. Mylan*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); and *Ex parte Ikeda*, App. No. 08/352,079, Appeal 2008-0492, Slip Op. at 7 (BPAI Mar. 26, 2008). For example, in *Takeda Chemical*, the post-*KSR* Federal Circuit noted that the recited compound, which was a modified version of compound b, was not recognized at the pertinent time as a suitable candidate for treatment of Type II diabetes. 492 F.3d at 1359. *Takeda Chemical* involved United States Patent No. 4,687,777, which was directed to a compound for the treatment of Type II diabetes. *Id.* at 1352-1354. The defendant argued that the patent was obvious in view of a reference that disclosed compound b, because the claimed compound could be synthesized from compound b by routine means. *Id.* at 1357. However,

[19] Declaration by Strauss at ¶ 1; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[20] Declaration by Strauss at ¶ 1; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

the Federal Circuit affirmed that the patent was not obvious because the prior art taught away from choosing compound b as a starting point. *Id.* at 1359-1361. Compound b was known to have unwanted side effects, and there was nothing in the prior art to suggest that homologation would decrease the unwanted side effects. *Id.* at 1359-1360.

In a more recent case, the Board reversed an examiner's rejection for failing to provide the requisite reason to combine the references. *Ikeda*, App No. 08/352,079 at 7. The *Ikeda* application was directed to a method of removing hydrocarbons from exhaust gases. *Id.* at 2. In pertinent part, the claims recited an absorption catalyst B located downstream of a catalyst A in the direction of the exhaust gas. The claims were rejected as unpatentable under 35 U.S.C. § 103 in view of Swaroop, Abe and Patil. *Id.* at 3. Swaroop taught positioning the absorption catalyst B upstream of catalyst A. *Id.* at 5. To remedy the deficiency in the art, the examiner cited "Patil and Abe as evidence of the 'coventionality of positioning the adsorbent catalyst 1 either upstream or downstream of a [three-way] catalyst 3' and thus conclude[d] that it would have been obvious to one of ordinary skill in this art to select an appropriate location for the adsorbent catalyst 16 in the apparatus of Swaroop ...." *Id.* at 5-6. The Board held that

> The Examiner has failed to provide any cogent reason or technical discussion to support the conclusion that one of ordinary skill in this art would have employed the relative positions of the catalysts in Abe and Patil without the use of the other teachings of these references, namely an auxiliary heater and bypass lines with valving. Second, the Examiner has not explained why one of ordinary skill in this art would have used the teachings of Patil, requiring bypass lines and valving, when Swaroop specifically ***teaches away*** from the use of valving and bypass lines [*citation omitted*]. Third, the Examiner has not supplied convincing reasoning or technical discussion to support the proposed switch in relative position of the catalysts when Swaroop specifically teaches that the exhaust gas is "modified" by the adsorbent catalyst and this modified form of the exhaust gas is *then* sent to the main or three-way catalyst to undergo conversion to innocuous products [*citation omitted*]. ... Fourth, the Examiner has not explained why one of ordinary skill in this art would have ***proceeded contrary to the teachings of Patil***, namely the teachings that "it is not possible merely to place zeolite 'in-line' in the exhaust system with the [main] catalyst has reached an effective temperature and unconverted hydrocarbons would still be discharged to the atmosphere" [*citation omitted*].

Emphasis added, *Ikeda*, App. No. 08/352,079 at 7.

Following the reasoning stated in *Takeda Chemical* and *Ikeda*, the Office Action must provide some explanation why one of ordinary skill in the art would believe that estetrol would be pharmacologically active when estetrol was believed to have too little estrogenic potency to be useful. As discussed above, prior to the publication of this invention, one of ordinary skill in the art would not expect estetrol to be pharmacologically active because it was known that estetrol was a considerably weaker estrogen than the already weak estrogen estriol.

It was not until the Applicants discovered estetrol's very long terminal elimination half-life that it became apparent that estetrol could be pharmacologically active. Prior to the disclosure of this invention, there was no publicly available data about the terminal elimination half-life of estetrol, about estetrol's binding to SHBG or about estetrol's effect on SHBG production.[21] Since estradiol and estriol have terminal elimination half-lifes of about 30 minutes and 5-10 minutes, respectively, it was believed that estetrol, another natural estrogen, would likewise have a short, if not shorter, terminal elimination half-life.[22] Unexpectedly, the Applicants discovered that estetrol has a terminal elimination half-life of about 28 hours.[23]

> A person of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only 1 hydroxy group and from estradiol by 2 hydroxy groups and (ii) both estriol and estetrol are produced during pregnancy. Hence, Applicants' finding that estetrol has a terminal elimination half-life that is 168-336 higher than that of the other pregnancy hormone estriol, was very unexpected and provided the clue towards its pharmacological usefulness.[24]

Like *Takeda Chemical*, one of ordinary skill in the art would have had no reason to use estetrol because it was believed not to be pharmacologically active. Maintaining a rejection based on the premise that estetrol can be used instead of estrone (E_1), estradiol (E_2) or estriol (E_3) is improper for the same reasons that the rejection in *Ikeda* was improper – because the prior art teaches away from using estetrol. As part of a *prima facie* case of obviousness, there must be some explanation why one of ordinary skill in the art

[21] Declaration by Coelingh Bennink at ¶¶ 4.

[22] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[23] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[24] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

would consider using estetrol when the prior art teaches that it is not pharmacologically active. Since such an explanation has not been provided, a *prima facie* case of obviousness has not been established. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Point II. It was unexpected to discover that estetrol was pharmacologically active.

Additionally, the unexpected result that estetrol is pharmacologically active because it has a long terminal elimination half-life rebuts the obviousness rejection. See *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311, (Fed. Cir. 2006); see also *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). To establish unexpected results, the Applicant must "establish (1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art, *In re Klosak*, 455 F.2d 1077, 59 CCPA 862 (1972); and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention, *Id.*; *In re D'Ancicco*, 439 F.2d 1244, 58 CCPA 1057 (1971)." *In re Freeman*, 474 F.2d 1318, 1324 (CCPA 1973). Without evidence to the contrary, an applicant need only provide substantially improved results and state that the results were unexpected. *Soni*, 54 F.3d at 750; *In re Lee*, App No. 10/091,061, 2007 WL 176690 at *3 (BPAI June 19, 2007).

In *Soni*, the examiner rejected certain claims as obvious in view of a combination of references. The applicant directed the examiner to the data in the specification, and argued that the increase in tensile strength and the increase in peel strength rebutted the rejections. *Soni*, 54 F.3d at 747. On appeal to the Federal Circuit, it was argued that the Board "could have taken judicial notice of the fact that higher molecular weight polymers would have been expected to tolerate higher filler loadings without degradation in properties and that it could have taken notice of the fact that it is the polymer *per se* that primarily determines the mechanical properties of a filled polymer composition." *Id.* at 750. However, the Federal Circuit found this argument fatally flawed because the Board failed to support its position with facts or evidence. *Id.* at 750; see also *Lee*, 2007 WL 176690 at *3. In summary, the Federal Circuit held that "[m]ere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected,*

this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Soni*, 54 F.3d at 751.

Estetrol has a terminal elimination half-life of 28 hours, which is 168-336 times greater than estriol's terminal half-life and about 56 times greater than estradiol's terminal half-life.[25] Thus, there is an actual difference and substantial improvement between estetrol and estriol as well as between estetrol and estradiol.

One of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only one hydroxyl group and from estradiol by two hydroxyl groups and (ii) both estriol and estetrol are produced during pregnancy.[26] Thus, one of ordinary skill in the art would have expected estetrol to have a terminal elimination half-life similar to estriol – on the order of a few minutes.[27] Unexpectedly, the Applicants discovered that estetrol's terminal elimination half-life was 28 hours.

The unexpectedly long terminal elimination half-life is associated with the unexpected pharmacological activity of estetrol. As discussed above, estetrol was known to be a very weak estrogen, so much so that it was dismissed by those of ordinary skill in the art as not being pharmacologically active.[28] Thus, it was unexpected to discover that estetrol, due to its unexpectedly long terminal elimination half-life, would be pharmacologically active.

Therefore, even assuming that a *prima facie* case of obviousness has been established, the unexpected results – that estetrol has an unexpectedly long terminal elimination half-life, and/or that estetrol is pharmacologically active – provide evidence that the recited invention is patentable over the cited references.

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[25] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[26] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[27] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[28] Declaration by Coelingh Bennink at Exhibit B.

AMENDMENTS TO THE SPECIFICATION

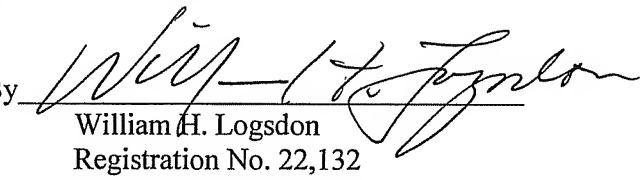
The Applicants have amended the specification to correct a typographical error. The originally filed specification referenced U.S. Patent Number 5,063,507. The '507 Patent is entitled "Goods database employing electronic title or documentary-type title," which is clearly not related to the invention disclosed in the specification for this application. The correct patent number is U.S. Patent Number 5,063,057. The Applicants have amended the specification accordingly.

CONCLUSION

Accordingly, Applicants respectfully request that the asserted rejections be reconsidered and withdrawn, and that claims 18-20, 24, 26, 28 and 32 be allowed.

Respectfully submitted,

THE WEBB LAW FIRM

By 

William H. Logsdon
Registration No. 22,132
Attorney for Applicants
436 Seventh Avenue
700 Koppers Building
Pittsburgh, PA 15219
Telephone: (412) 471-8815
Facsimile: (412) 471-4094
E-mail: webblaw@webblaw.com